# FDA Perspective on International Clinical Trials

**Kassa Ayalew, M.D., M.P.H.**

Acting Branch Chief
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
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# Disclaimer

**The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration.**

# Outline

- Trends in The Globalization of Clinical Research (CR)
- Driving Forces
- Regulatory Challenges
- FDA's Strategies
- Final Thoughts

# Globalization of CR

- CR has traditionally been carried out in wealthy countries
- Shift in CR sponsored by pharmaceutical & device companies to emerging regions is increasing
- Medical product discovery & development are becoming increasingly globalized
- The shift in the business model presents regulatory challenges-from product development to use by consumers

# Globalization of CR (cont)

**Clinical trials are increasingly conducted outside US**

- In 2007: over 60% of pivotal studies submitted to CDER contained data from one or more foreign study sites ( 6 out of 10 of the studies)
- Foreign studies/data are also increasing in biologics & medical device applications

# Globalization of CR (cont)

- From October 2007 to Sept 2008, clinical trials for medical products were conducted at nearly 6,500 foreign sites
  - Western Europe accounted for 60% of total non-US sites
  - The other 40% was nearly evenly divided:
    - Eastern Europe: 11%
    - Asia/Pacific: 10%
    - Non-U.S. North America: 8%
    - Central/South America: 8%

U.S. Department of Health and Human Services. 2010. Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials. Retrieved June 16, 2011, from http://oig.hhs.gov/oei/reports/oei-01-08-00510.p

# What Drives Companies to Conduct Clinical Trials Outside the USA?

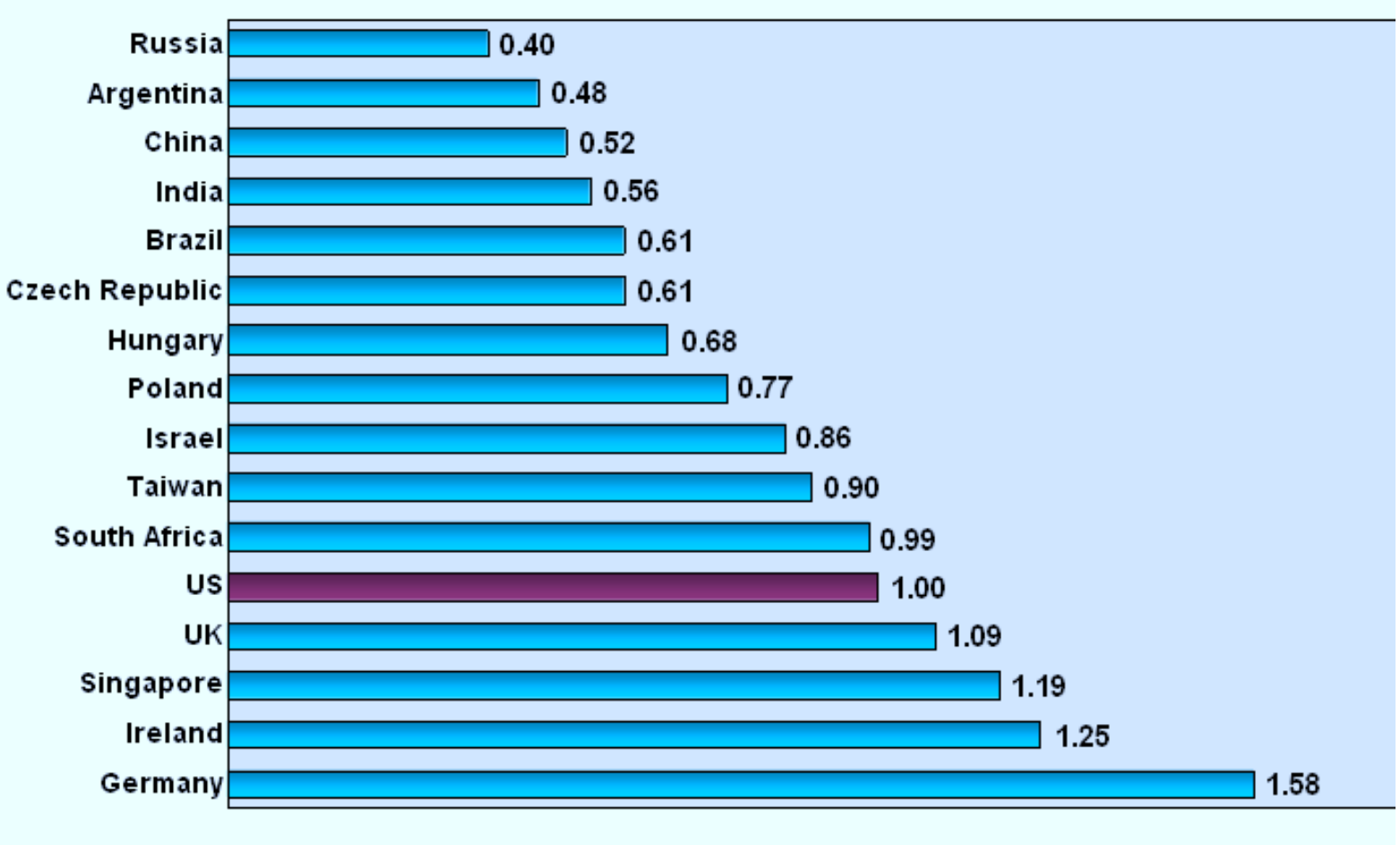
# Pulling Forces

- Lower operational costs (clinical, salaries, rental)
- Availability of large # of patients
  - Rx naïve subjects willing & eager to participate
- Availability of CROs focused on global trials
- Faster recruitment rates/ short timeline
- Fewer logistical problems (contract & bureaucracy, reduced regulatory barriers)
- Widespread adoption of the (ICH-GCP) guidelines & stronger intellectual property protections

# Pushing Forces

- **Difficulty recruiting patients**
  - Fewer feel need to participate
  - Higher standard of care
  - Mistrust (historical infamy Tuskegee trial)
  - Requirement for larger # of Pts
  - Insurance precluding participation/Liability /HIPAA
- **Economic Drivers**
  - Costs: clinical care/Operational/bureaucratic (compliance, documentation & training)

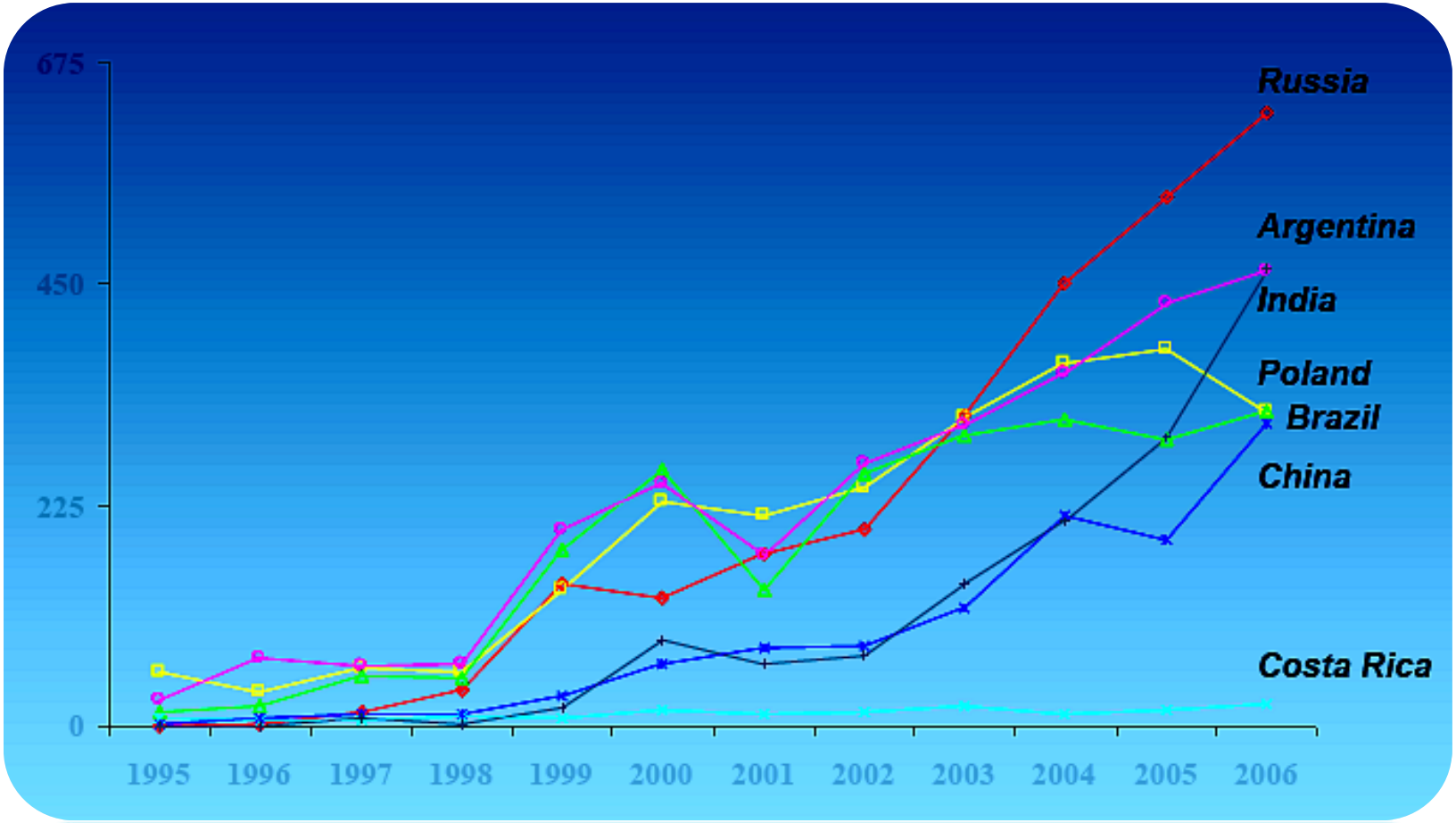
# Overall Clinical Trial Costs




- **The cost of conducting CR in Russia, Argentina, China & India is about half the cost to the US ( manpower, rental, IT & operational costs)**

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)

# Annual Growth in Clinical Investigations




**Increasing Annual Growth of Clinical Trials Outside the US**

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)

# The Rate of Increase for FDA Regulated Investigators Around the Globe

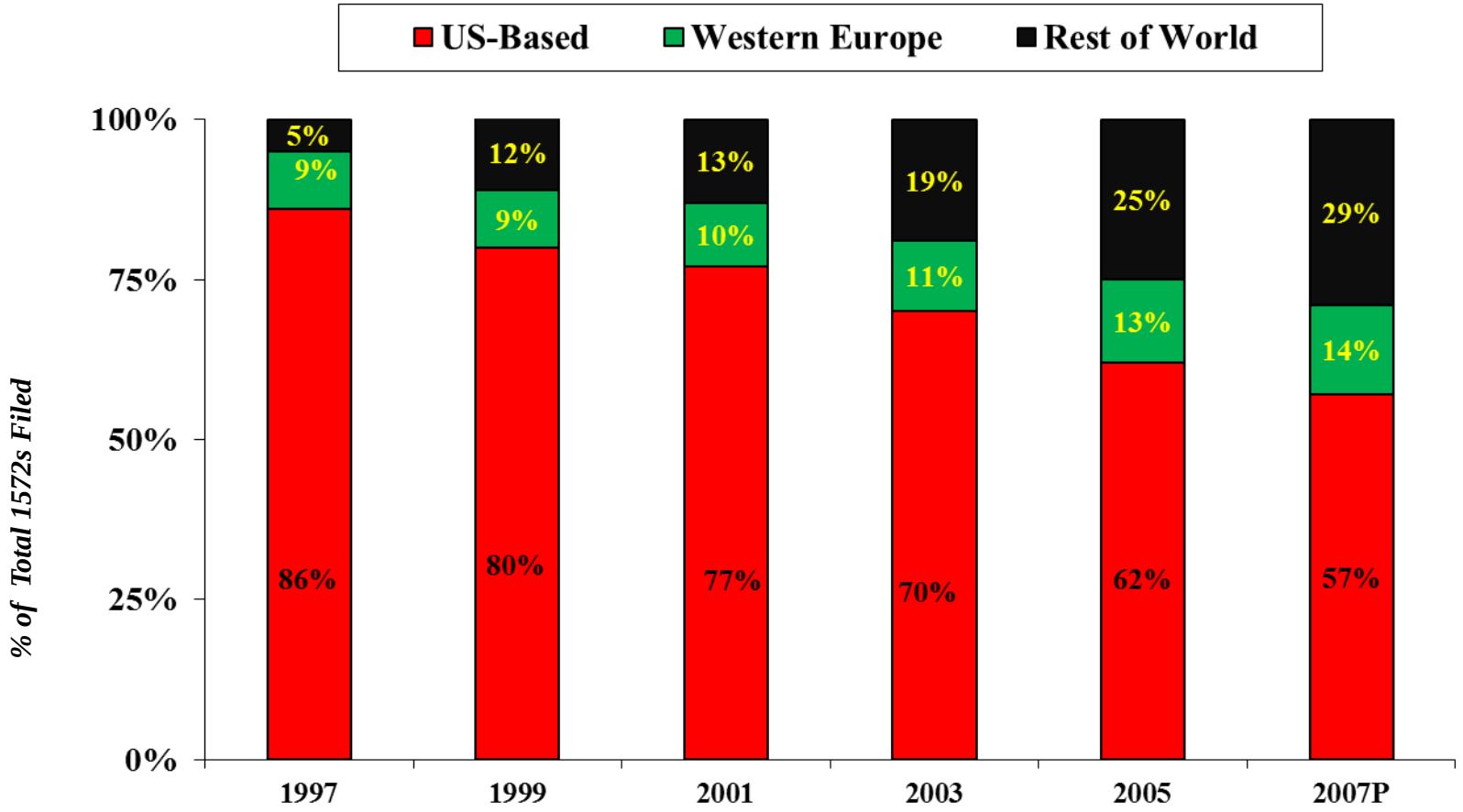
| | 1996 | Percent of Total | 2006 | Percent of Total | Annualized 10-year Growth Rate |
|---|---|---|---|---|---|
| North America | 12,174 | 83.65% | 14,555 | 63.18% | 1.80% |
| Western Europe | 1899 | 13.05% | 3923 | 17.03% | 7.52% |
| Central and Eastern Europe | 56 | 0.38% | 1793 | 7.78% | 41.4% |
| Latin America | 98 | 0.67% | 1095 | 4.75% | 27.3% |
| Asia | 108 | 0.74% | 1054 | 4.58% | 25.6% |
| Rest of World | 218 | 1.50% | 617 | 2.68% | 11.0% |
| TOTAL | 14,574 | | 23,089 | | |

**Source:** Tufts Center for the Study of Drug Development.

- **During the 10 year period, the % of total for UAS based investigators declined by 20% (annual growth rate 1.8%)**
- **The number of active FDA–regulated investigators based outside the United States has grown**

http:// appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Regulatory/Global-Clinical-Trials-Activity-in-the-Details/ArticleStandard/Article/detail/453243?ref=25

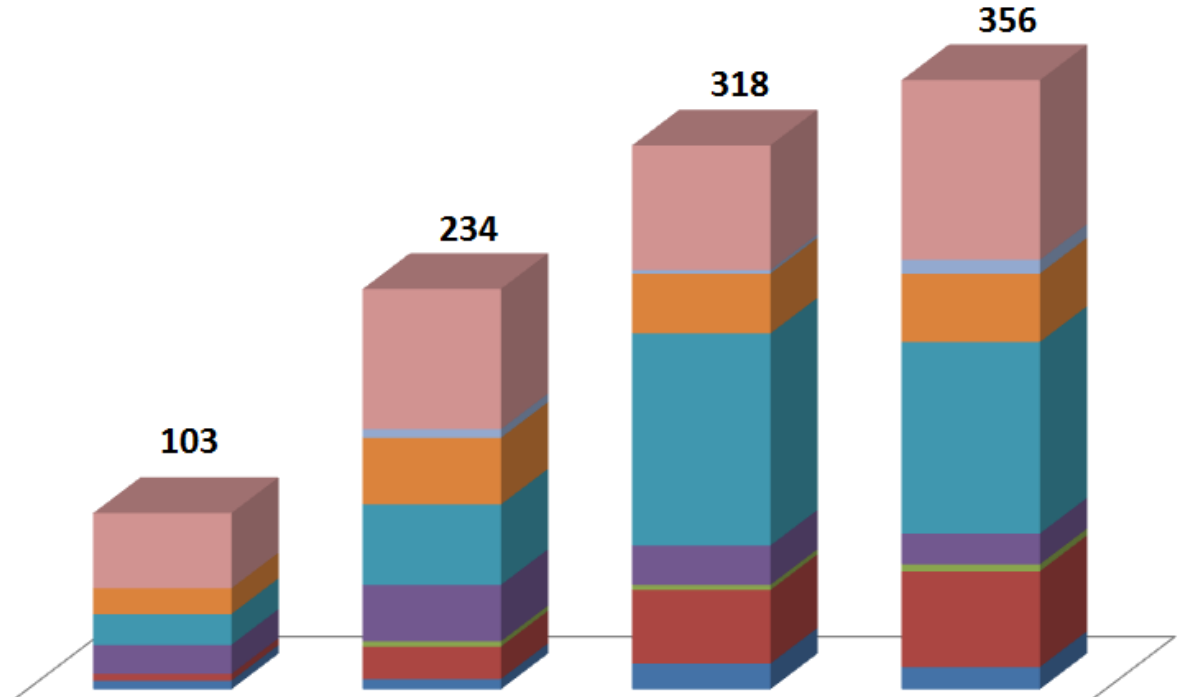
# Globalization of Clinical Investigators




Sources: Tufts CSDD

**Dramatic shift in the location of clinical trials**

# Growth in Foreign CI Inspections




| | FY'01-FY'03 | FY'04-FY'06 | FY'07-FY'09 | FY'10-FY'12 |
|---|---|---|---|---|
| Western Europe | 44 | 82 | 73 | 105 |
| Middle East/Central Asia | 0 | 5 | 2 | 8 |
| Latin America/Caribbean | 15 | 39 | 35 | 40 |
| Eastern Europe | 18 | 47 | 124 | 112 |
| Canada | 17 | 33 | 23 | 18 |
| Australia-Oceania | 0 | 3 | 3 | 4 |
| Asia/Pacific | 4 | 19 | 43 | 56 |
| Africa | 5 | 6 | 15 | 13 |

* Based on Inspection start date in CDER/OC/OSI database as of September 3, 2013

# The increasing number of foreign clinical trials conducted outside US presents FDA with many challenges

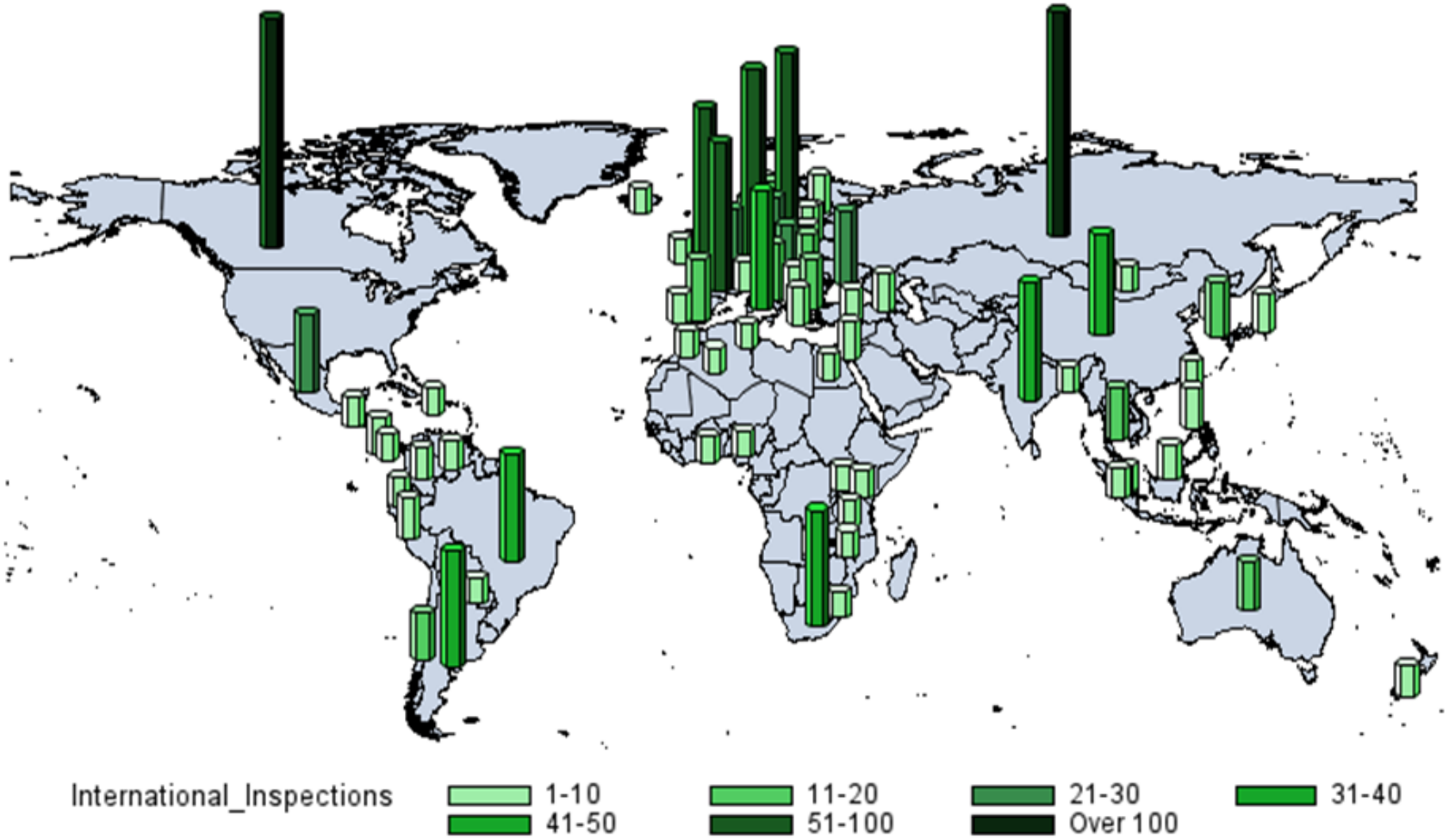
# Use of Foreign Data to Support Marketing Applications

- Governed by 21 CFR 312.120, 314.106, 814.15
- Data will be acceptable if
  - FDA is able to validate data
  - Competent clinical investigators
  - Conducted in accordance with GCPs, including independent ethics board review, approval, continuing oversight
  - Data is applicable to the US population & medical practice

# Regulatory Challenges

- The need to do GCP inspections in many parts of the world
  - Increased resources (personnel, language/translation etc),
- Need to assess qualifications & legislation
  - Increased knowledge of various medical qualifications & medical practice legislation from many countries
- More demand in interactions with counterpart regulatory authorities when need arises (ex. safety)
  - Confidentiality Arrangements

# Global Coverage of FDA CDER GCP Inspections*




* Conducted for FDA/CDER from 1984 through Sept 3, 2013; Based on Inspections with a start date in CDER/OC/OSI database

# Challenges (cont)

- **Ethical Conduct**
  - Difference in definition of legitimate "consent" ( illiteracy, difference in legal rights by gender or age)
  - Wide disparities in "standard of care" /patient access to healthcare/availability of Rx

# Challenges(cont)

- **Relevance of the study population in foreign sites to the US population & medical practice**
  - Intrinsic (genetic variants ass'd with response) / Extrinsic factors (medical practice, disease definition & study population)
  - Underlying illnesses/Concomitant therapies
  - Cultural issues – food, dietary supplements, herbals, adherence, reporting AEs

# FDA is embracing a wide variety of strategies to address the challenges in international clinical trials

# Strategies

**Harmonizing Science-Based Standards**

- Working to harmonize regulatory standards (to share a common foundation of science-based goals for product safety, quality, and efficacy).

- Continue to work to harmonize regulatory standards, processes, and procedures for the pharmaceutical industry( ex. ICH, ICH Global Cooperation Group Members)

# Strategies(cont)

**Leveraging Knowledge and Resources**

- Utilize finite resources strategically and efficiently, leverage inspection resources ( Observe each other inspection, conducting joint inspection, provide parallel advice to sponsors, participate in regular discussions)
- Share knowledge and information (inspection reports)
  - European Medicines Agency (EMA), European National Inspectorates, Health Canada, Japan's PDMA, Korea's KFDA, China's SFDA, Singapore's HAS, Argentina's ANMAT, New Zealand, South Africa, Israel, India, Jordan, Thailand

U.S. Food and Drug Administration

European Commission

European Medicines Agency

# Strategies(cont)

**Advancing Regulatory Science**

- Actively engaging with global partners to harness scientific developments, resources, & brainpower to support science-based regulatory decision-making & pursue the best possible public health solutions

- CBER scientists developed a high-efficiency conjugation method to develop vaccine against meningitis, donated the technology to Meningitis Vaccine Project.
- Trained scientists , worked to help produce the vaccine
- The vaccine would end meningitis epidemics in the 25 African countries of the “meningitis belt” forever

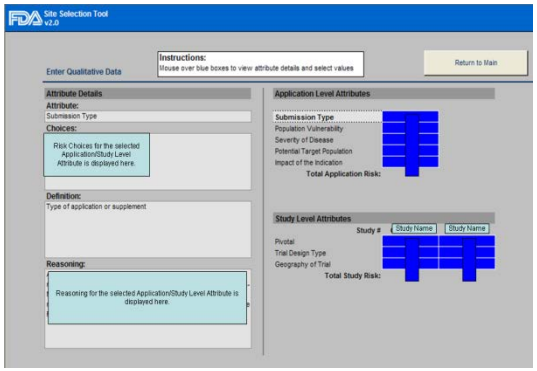
# Strategies(cont)

**Risk-Based Monitoring and Inspection**

- Using innovative strategies & tools to identify sites for clinical inspection(ex. GCP risk-based site selection tool for clinical inspection)

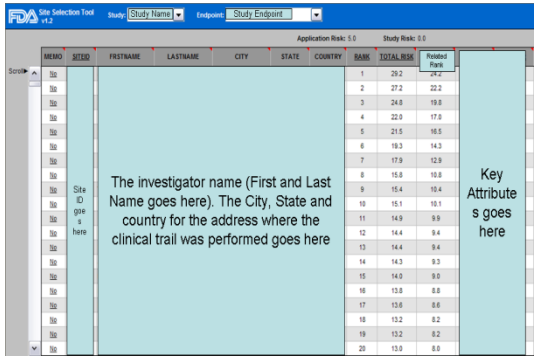
# Risk-Based Site Selection Tool

## •1 Enter Qualitative Attributes



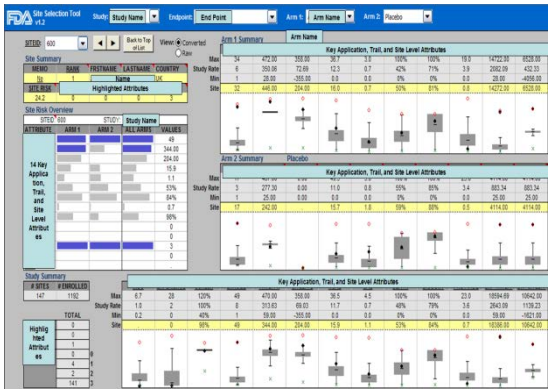

•OND and DSI reviewers assign Study & Application level risk

## •2 View High-level Outputs



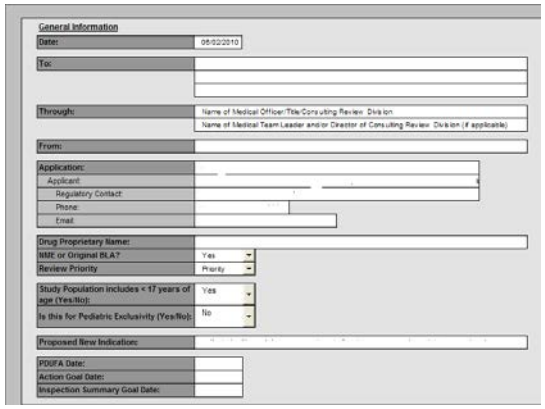

•Risk-ranked output of site with ability to assign site for inspection & see further details

## •3 View Detailed Site Outputs




•Site-level details w/ comparative analysis among treatment arms and other sites in study

## •4 Generate Consult Form




•Automated generation of DSI Consult form with sites selected from tool

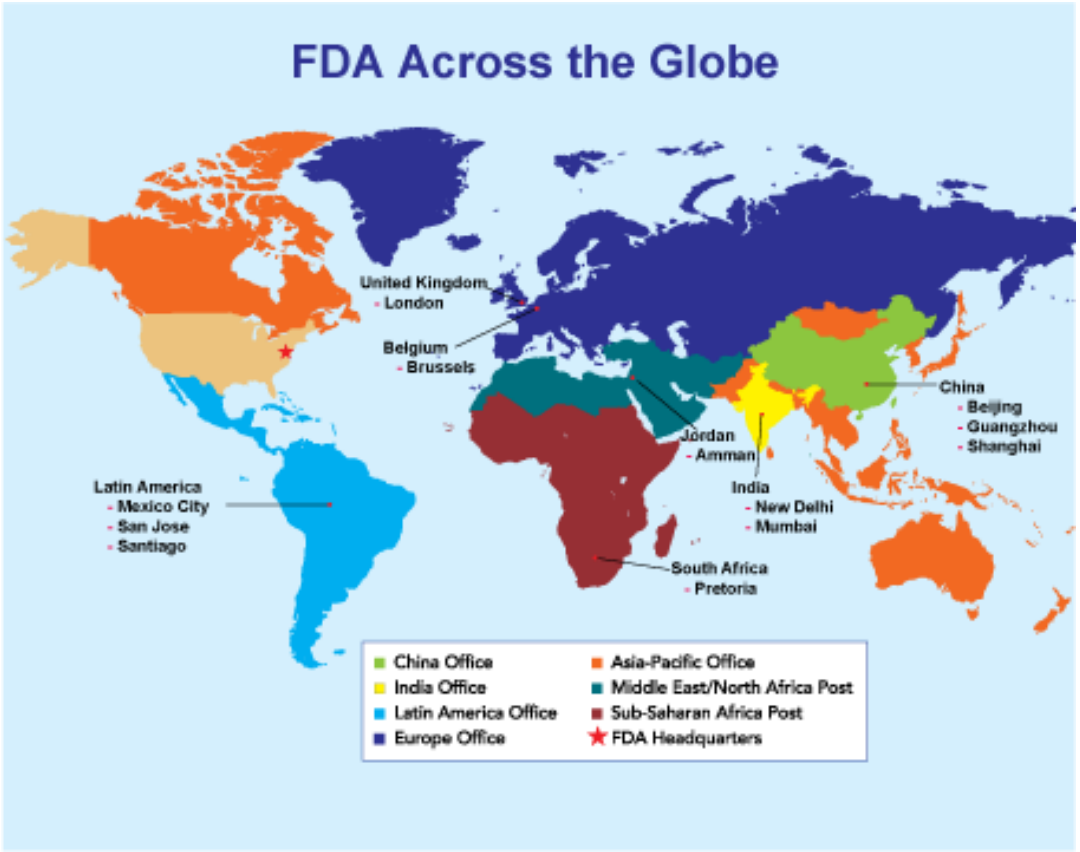
**GCP tool provides risk-ranked information about clinical sites**

# Building Quality in CR

- **Build quality in during the planning stages:**
  - incorporate into a study ways to prevent the critical/errors, and monitor for those errors (perhaps centrally (remotely/real time)) and focus less on the less important matters

# Strategies(cont)

## FDA International Offices




- Offices collect & leverage local & regional knowledge
- Provide a platform for inspection of foreign facilities

# Strategies(cont)

## Strengthening Regulatory Capacity


**Commencement of the Peking University 2011 Master's Degree Program in International Pharmaceutical Engineering Management.**

- Strengthening capacity of governments to manage, assess, and regulate drug development ( such as providing information, tools, training & exchange programs)

# Final Thought

"Wherever you stand, the majority of clinical trials are being conducted elsewhere, and yet we all as regulators use these data to allow or disallow marketing of a product, and physicians and patients use these data to decide to use or not use a medicine."

*Fergus Sweeney, EMA*

"Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders."

*Margaret Hamburg, FDA Commissioner*

kassa.ayalew@fda.hhs.gov